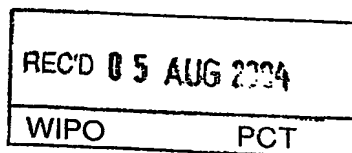




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23JUN03 E816814-1 D02029  
P01/7700 0.00-0314488.8

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

20 JUN 2003

The Patent Office  
Cardiff Road  
Newport  
Gwent NP9 1RH

1. Your reference

PAB/JP/NM/PB60321P

2. Patent application number

(The Patent Office will fill in his part)

0314488.8

3. Full name, address and postcode of the or of each applicant (*underline all surnames*)

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited  
Glaxo Wellcome House, Berkeley Avenue,  
Greenford, Middlesex UB6 0NN, Great Britain

00473587003.  
United Kingdom

4. Title of the invention

Therapeutically Useful Compounds

5. Name of your agent (*if you have one*)

"Address for service" in the United Kingdom to which all correspondence should be sent

(*including the postcode*)

Patents ADP number (*if you know it*)

08072555004

Corporate Intellectual Property

GlaxoSmithKline  
Corporate Intellectual Property (CN9 25.1)  
980 Great West Road  
BRENTFORD  
Middlesex TW8 9GS

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (*if you know it*) the or each application number

Country	Priority application number ( <i>if you know it</i> )	Date of filing ( <i>day / month / year</i> )
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing ( <i>day / month / year</i> )
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer yes if:*

- a) any applicant named in part 3 is not an inventor, or
  - b) there is an inventor who is named as an applicant, or
  - c) any named applicant is a corporate body
- See note (d)

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Continuation sheets of this form	0
Description	21
Claim(s)	4
Abstract	1
Drawings	0

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11.

We request the grant of a patent on the basis of this application

Signature Judith Pritchard Date 19-Jun-03  
J Pritchard

12. Name and daytime telephone number of person to contact in the United Kingdom

J Pritchard 01438 768610

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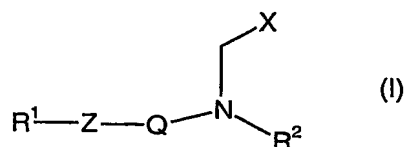
# Therapeutically Useful Compounds

This invention relates to novel chemical compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

The compounds of the invention are inhibitors of matrix metalloproteinase enzymes (MMPs).

Matrix metalloproteinase enzymes play a major role in extracellular matrix component degradation and remodelling. Examples of MMPs include collagenase 1, 2 and 3, gelatinase A and B, stromelysin 1, 2 and 3, matrilysin, macrophage metalloelastase, enamelysin and membrane type 1, 2, 3 and 4 MMP. The enzymes are secreted by connective tissue cells and inflammatory cells. Enzyme activation can not only initiate tissue damage but induce increased inflammatory cell infiltration into the tissue, leading to more enzyme production and subsequent tissue damage. For example, elastin fragments produced by MMP degradation are believed to stimulate inflammation by attracting macrophages to the site of MMP activity. Inhibition of MMPs provides a means for treating disease states wherein inappropriate metalloprotease activity results in degradation of connective tissue and inflammation.

In one aspect, the present invention provides compounds of formula (I):



wherein

R<sup>1</sup> represents optionally substituted C<sub>4-12</sub> alkyl, optionally substituted C<sub>2-6</sub>alkylaryl, or optionally substituted 5- or 6- membered aryl or heteroaryl;

Z represents a bond, CH<sub>2</sub>, O, S, SO, SO<sub>2</sub>, NR<sup>4</sup>, OCR<sup>4</sup>R<sup>5</sup>, CR<sup>4</sup>R<sup>5</sup>O, or Z, R<sup>1</sup> and Q together form an optionally substituted fused tricyclic group;

Q represents an optionally substituted 5- or 6- membered aryl or heteroaryl ring;

X represents COR<sup>3</sup> or N(OR<sup>6</sup>)COR<sup>9</sup>;

R<sup>2</sup> represents SO<sub>2</sub>R<sup>10</sup> or SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>;

R<sup>3</sup> represents OR<sup>6</sup>, NR<sup>6</sup>R<sup>7</sup> or NR<sup>6</sup>OH;

R<sup>4</sup> and R<sup>5</sup> each independently represents H, C<sub>1-6</sub> alkyl or C<sub>1-4</sub> alkylaryl;

R<sup>6</sup> and R<sup>7</sup> each independently represents H, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted with one or

more heteroaryl groups, or  $R^6$  and  $R^7$  together with the nitrogen atom to which they are attached form a 5- or 6- membered ring which may optionally include 1 or more further heteroatoms selected from O, S and N;

$R^8$  and  $R^9$  each independently represents H or  $C_{1-6}$  alkyl;

5  $R^{10}$  and  $R^{11}$  each independently represents H or  $C_{1-6}$  alkyl; and

and physiologically functional derivatives thereof, with the exception of N-(ethoxycarbonyl)-N-[4-(1H-tetrazol-1-yl)phenyl]glycine.

10 References to 'aryl' include references to monocyclic carbocyclic aromatic rings (e.g. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) and references to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-3 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. pyridinyl, pyrimidinyl, thiophenyl, furanyl, pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl or imidazolyl, and examples of bicyclic  
15 heterocyclic aromatic rings include e.g. benzimidazolyl, quinolinyl or indolyl. Carbocyclic and heterocyclic aromatic rings may be optionally substituted, e.g. by one or more  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl, halogen,  $(CH_2)_{0-4}OR^6$ ,  $(CH_2)_{0-4}SR^6$ ,  $SO_2R^6$ ,  $COR^6$ , aryloxy, thioaryl, cyano, hydroxy, nitro,  $NR^6R^7$ ,  $-NR^6COR^7$ ,  $-OCF_3$ ,  $-CF_3$ ,  $COOR^7$ ,  $-OCHCF_2$ ,  $-SCF_3$ ,  $-CONR^6R^7$ ,  $-SO_2NR^6R^7$ , or like groups.

20 References to 'alkyl' include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to 'alkylene' and 'alkoxy' shall be interpreted similarly.

25 Preferably,  $R^1$  represents aryl, more preferably substituted or unsubstituted phenyl.

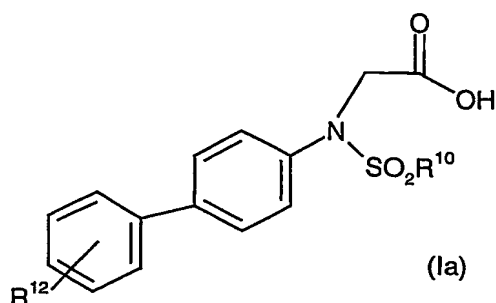
Preferably  $R^2$  represents  $SO_2R^{10}$ , more preferably  $SO_2CH_3$ .

Preferably  $R^3$  represents OH or  $NR^6R^7$ . Most preferably X represents  $CO_2H$ .

Preferably Z represents a bond.

30 When  $R^6$  or  $R^7$  represents  $C_{1-6}$ alkyl substituted with one or more heteroaryl groups, it is preferred for the  $C_{1-6}$  alkyl group to be methyl or ethyl; it is preferred for the alkyl group to be substituted with one heteroaryl group. Preferably, one of  $R^6$  or  $R^7$  represents H.

A preferred subgroup of compounds of formula (I) is represented by formula (Ia):



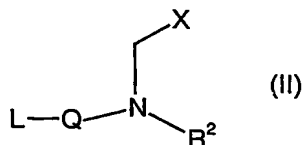
- 5 wherein  $R^{10}$  represents H or  $C_{1-6}$  alkyl, preferably  $C_{1-4}$  alkyl, most preferably methyl;  
 $R^{12}$  represents H, halo,  $CF_3$ , cyano,  $OCF_3$ , nitro,  $OR^{13}$ ,  $SR^{13}$  or  $COR^{13}$ ;  
 $R^{13}$  represents H,  $C_{1-6}$  alkyl or  $C_{1-4}$  alkylaryl;  
 and physiologically functional derivatives thereof.
- 10 Preferably  $R^{12}$  is in the meta or para position. Most preferably  $R^{12}$  is in the para position.
- By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto and includes any
- 15 pharmaceutically acceptable esters, amides and carbamates, salts and solvates of compounds of formula (I) which, upon administration to the recipient, are capable of providing (directly or indirectly) compounds of formula (I) or active metabolite or residue thereof.
- 20 Salts of compounds of formula (I) are also provided by the invention. Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides,
- 25 sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates.

Examples of solvates include hydrates.

When compounds of formula (I) contain chiral centres, the invention extends to mixtures of enantiomers (including racemic mixtures) and diastereoisomers as well as to individual enantiomers. Generally it is preferred to use a compound of formula (I) in the form of a purified single enantiomer.

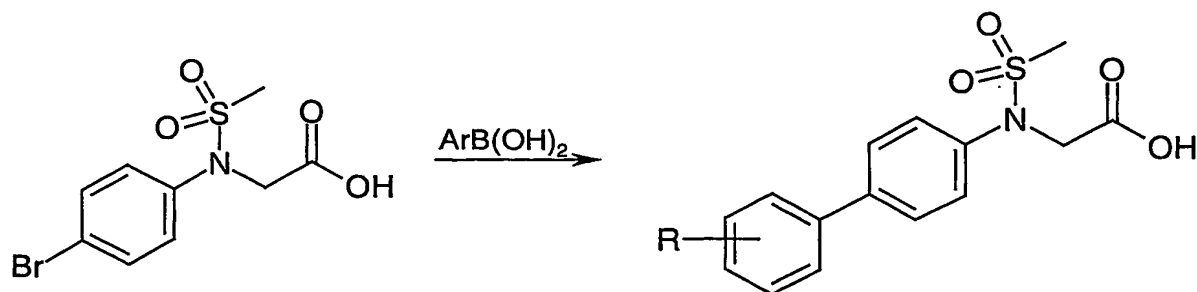
The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A first process (A) according to the invention for preparing a compound of formula (I) wherein Z represents a bond and R<sup>1</sup> represents an optionally substituted C<sub>2-6</sub>alkylaryl or an optionally substituted 5- or 6- membered aryl or heteroaryl, comprises reacting a compound of formula (II):



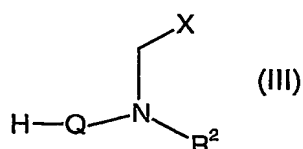
wherein R<sup>2</sup>, Q and X are as previously defined for formula (I) and L represents a leaving group, with a reagent suitable to introduce the group R<sup>1</sup>, such as a compound R<sup>1</sup>B(OH)<sub>2</sub>, suitably in the presence of a catalyst, such as a noble metal catalyst e.g. palladium, and a suitable base, such as an alkali metal carbonate, e.g. caesium carbonate. The reaction is conveniently carried out in a suitable solvent, such as a polar organic solvent, e.g. dimethyl formamide. Suitable leaving groups represented by L include halides, especially bromide or iodide.

For example, for the synthesis of a (optionally substituted) [(1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid according to the invention a phenyl boronic acid may be reacted with [(4-bromophenyl)(methylsulfonyl)amino]acetic acid in the presence of a suitable catalyst:



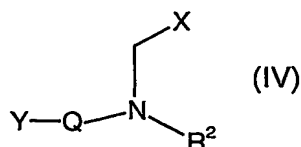
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A second process (B) according to the invention for preparing a compound of formula (I) wherein Z represents a bond and  $\text{R}^1$  represents an optionally substituted  $\text{C}_{4-12}$ alkyl, comprises reacting a compound of formula (III):



10 wherein  $\text{R}^2$ ,  $\text{Q}$  and  $\text{X}$  are as previously defined for formula (I), with a reagent suitable to introduce the group  $\text{R}^1$ , such as a compound  $\text{R}^1\text{-L}$ , wherein  $\text{L}$  is a suitable leaving group, for example halide, suitably in the presence of a catalyst, for example a Lewis acid catalyst such as  $\text{AlCl}_3$ . A Friedel-Crafts reaction may accordingly be appropriate.

15 A third process (C) according to the invention for preparing a compound of formula (I) wherein Z represents O, S, SO,  $\text{SO}_2$ ,  $\text{NR}^4$  or  $\text{OCR}^4\text{R}^5$ , and  $\text{R}^1$  represents an optionally substituted  $\text{C}_{4-12}$ alkyl comprises reacting a compound of formula (IV):



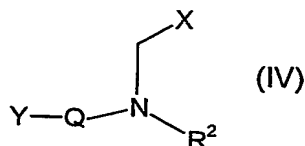
20 wherein  $\text{X}$ ,  $\text{R}^2$  and  $\text{Q}$  are as previously defined for formula (I), and  $\text{Y}$  represents  $\text{OH}$ ,  $\text{SH}$ ,  $\text{NR}^4\text{H}$  or  $\text{HOOCR}^4\text{R}^5$ , with a reagent suitable to introduce the group  $\text{R}^1$ , such as a compound  $\text{R}^1\text{-L}$ , wherein  $\text{L}$  is a suitable leaving group. The reaction is conveniently carried out in a suitable solvent, such as an alcohol solvent, e.g. ethanol, under basic conditions, for



example in the presence of an aqueous hydroxide such as sodium hydroxide. Suitable leaving groups represented by L include halides, especially bromide or iodide.

For compounds in which Z represents SO or SO<sub>2</sub>, the compound of formula (I) may conveniently be prepared by initial preparation of the compound in which Z represents S, followed by oxidation of the sulphide to the sulfoxide or the sulfone. The oxidation step may be carried out using methods known in the art such as oxidation with hydrogen peroxide in the case of the sulfone, or oxidation with Oxone® (potassium peroxymonosulfate) in the case of the sulfoxide.

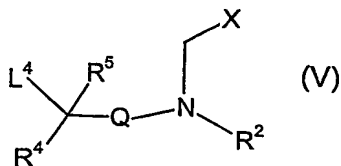
A fourth process (D) according to the invention for preparing a compound of formula (I) wherein Z represents O, S, SO, SO<sub>2</sub>, or NR<sup>4</sup>, and R<sup>1</sup> represents an optionally substituted C<sub>2</sub>-alkylaryl or an optionally substituted 5- or 6- membered aryl or heteroaryl, comprises reacting a compound of formula (IV):



wherein X, R<sup>2</sup> and Q are as previously defined for formula (I), and Y represents OH, SH or NR<sup>4</sup>H, with a reagent suitable to introduce the group R<sup>1</sup>, such as a compound R<sup>1</sup>-L, wherein L is a suitable leaving group. The reaction is conveniently carried out in a suitable solvent, such as a solvent containing a heteroatom, e.g. pyridine, in the presence of a suitable catalyst, for example palladium catalyst (preferred for Y = NR<sup>4</sup>H) or a copper catalyst (preferred for Y = OH or SH). Suitable leaving groups represented by L include halides, especially bromide or iodide.

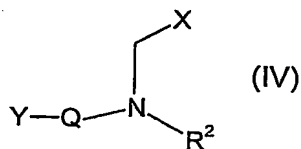
For compounds in which Z represents SO or SO<sub>2</sub>, the compound of formula (I) may conveniently be prepared by initial preparation of the compound in which Z represents S, followed by oxidation of the sulphide to the sulfoxide or the sulfone. The oxidation step may be carried out using methods known in the art such as oxidation with hydrogen peroxide in the case of the sulfone, or oxidation with Oxone® (potassium peroxymonosulfate) in the case of the sulfoxide.

A fifth process (E) according to the invention for preparing a compound of formula (I) wherein Z represents  $\text{OCR}^4\text{R}^5$  and  $\text{R}^1$  represents an optionally substituted  $\text{C}_{2-6}$ alkylaryl or an optionally substituted 5- or 6- membered aryl or heteroaryl, comprises reacting a compound of formula (V):



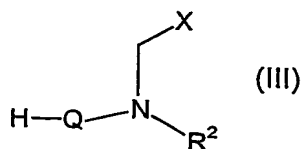
wherein X,  $\text{R}^2$  and Q are as previously defined for formula (I) and  $\text{L}^4$  is a suitable leaving group, with a reagent suitable to introduce the group  $\text{R}^1\text{-O}$  such as a compound  $\text{R}^1\text{-OH}$ . The reaction is conveniently carried out in a suitable solvent, such as an alcohol solvent, e.g. ethanol, under basic conditions, for example in the presence of an aqueous hydroxide such as sodium hydroxide. Suitable leaving groups represented by  $\text{L}^4$  include halides, especially bromide or iodide.

A sixth process (F) according to the invention for preparing a compound of formula (I) wherein Z represents  $\text{CR}^4\text{R}^5\text{O}$ , comprises reacting a compound of formula (IV) :



wherein X,  $\text{R}^2$  and Q are as previously defined for formula (I), and Y represents OH, with a reagent suitable to introduce the group  $\text{R}^1\text{CR}^4\text{R}^5$  such as a compound  $\text{R}^1\text{CR}^4\text{R}^5\text{-L}$ , wherein L is a suitable leaving group. The reaction is conveniently carried out in a suitable solvent, such as an alcohol solvent, e.g. ethanol, under basic conditions, for example in the presence of an aqueous hydroxide such as sodium hydroxide. Suitable leaving groups represented by L include halides, especially bromide or iodide.

A seventh process (G) according to the invention for preparing a compound of formula (I) wherein Z represents  $\text{CH}_2$ , comprises reacting a compound of formula (III):



wherein  $R^2$ , Q and X are as previously defined for formula (I), with a reagent suitable to introduce the group  $R^1CH_2$ , such as a compound  $R^1CH_2-L$ , wherein L is a suitable leaving group, for example halide, suitably in the presence of a catalyst, for example a Lewis acid catalyst such as  $AlCl_3$ . A Friedel-Crafts reaction may accordingly be appropriate.

5

An eighth process (H) according to the invention comprises carrying out a process selected from processes (A) to (G) followed by interconversion of one or more functional groups.

10

Compounds of formula (II) may be prepared for example by reaction of a compound of formula  $L-Q-NH-CH_2X$  (formula (VI)) with a compound of formula  $R^2-L^2$  wherein L, Q, X and  $R^2$  are as previously defined for formula (II) and  $L^2$  represents a leaving group, in the presence of a base. In turn compounds of formula (VI) may be prepared by reaction of a compound of formula  $L-Q-NH_2$  with a compound of formula  $X-CH_2L^3$  wherein L, Q and X are as previously defined and  $L^3$  represents a leaving group. The reaction is preferably carried out in a polar organic solvent (for example dimethyl formamide) in the presence of a base (for example potassium carbonate).

15

20

Compounds of formula (III) may be prepared in an analogous fashion to compounds of formula (II) starting from a compound of formula  $H-Q-NH-CH_2X$  (formula (VII)) in place of a compound of formula (VI). In turn compounds of formula (VII) may be prepared by reaction of a compound of formula  $H-Q-NH_2$  with a compound of formula  $X-CH_2L^3$  wherein Q and X are as previously defined and  $L^3$  represents a leaving group. The reaction is preferably carried out in a polar organic solvent (for example dimethyl formamide) in the presence of a base (for example potassium carbonate).

25

30

Similarly, compounds of formula (IV) may be prepared in an analogous fashion to the compounds of formula (II) starting from a compound of formula  $Y-Q-NH-CH_2X$  (formula (VIII)) wherein Y represents OH, SH,  $NR^4H$  or  $HCR^4R^5$ , in place of a compound of formula (VI). In turn compounds of formula (VIII) may be prepared by reaction of a compound of formula  $Y-Q-NH_2$  with a compound of formula  $X-CH_2L^3$  wherein Y, Q and X are as previously defined and  $L^3$  represents a leaving group. The reaction is preferably carried out in a polar organic solvent (for example dimethyl formamide) in the presence of a base (for example potassium carbonate).

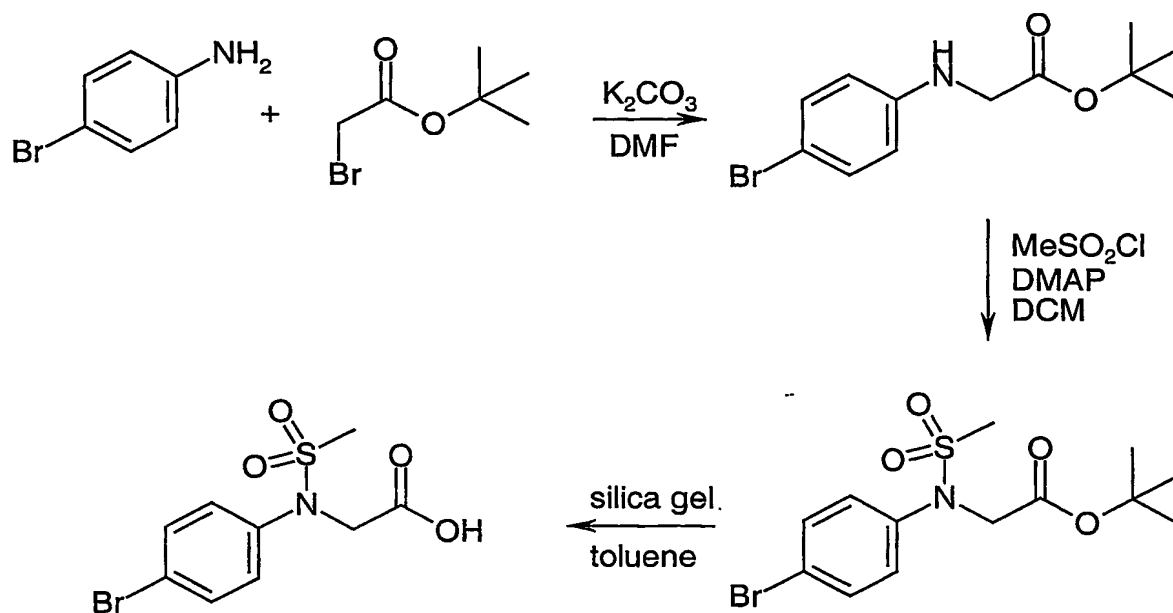
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Similarly, compounds of formula (V) may be prepared in an analogous fashion to the compounds of formula (II) starting from a compound of formula  $L^4CR^4R^5-Q-NH-CH_2X$  (formula (IX)) in place of a compound of formula (VI). In turn compounds of formula (IX) may be prepared by reaction of a compound of formula  $L^4CR^4R^5-Q-NH_2$  with a compound of formula  $X-CH_2L^3$  wherein  $L^4$ , Q and X are as previously defined and  $L^3$  represents a leaving group. The reaction is preferably carried out in a polar organic solvent (for example dimethyl formamide) in the presence of a base (for example potassium carbonate).

Compounds of formula  $R^2-L^2$ ,  $L-Q-NH_2$ ,  $X-CH_2L^3$ ,  $H-Q-NH_2$ ,  $Y-Q-NH_2$ , and  $L^4CR^4R^5-Q-NH_2$  are known or may be prepared by known methods.

Depending on the identity of the group X, it may be preferable for that group to be protected during the steps of the synthesis of a compound of formula (II). Suitable protecting groups are known to those skilled in the art. Protecting groups may be any conventional protecting groups, for example as described in "Protective Groups in Organic Synthesis" by Theodora Greene and Peter G.M. Wuts (John Wiley and Sons Inc. 1999). Suitable carboxylic acid protecting groups include but are not limited to carboxylic acid esters, for example, methyl ester, ethyl ester, t-butyl ester, aryl esters e.g. benzyl ester.

For example, a compound of formula (II) in which X is  $COR^3$ ,  $R^3$  is OH,  $R^2$  is  $SO_2Me$ , Q is phenyl and L is 4-bromo may be prepared by the following scheme in which the free acid group of the final product is protected as the t-butyl ester during the synthesis substitution reactions:



It will be appreciated by those skilled in the art that compounds of formula (I) may also be prepared from other compounds of formula (I) by interconversion using processes such as oxidation, reduction, substitution, deprotection etc., standard in the art of synthetic chemistry.

The enantiomeric compounds of the invention may be obtained (a) by the separation of the components of the corresponding racemic mixture, for example, by chiral chromatography, enzymatic resolution methods or preparing and separating suitable diastereoisomers, (b) by direct synthesis from the appropriate chiral starting materials by the methods described above, or (c) by methods analogous to those described above using chiral reagents.

Optional conversion of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or other physiologically functional derivative may be effected by methods known to those skilled in the art.

Compounds of formula (I) may be useful for the treatment of any conditions in which inhibition of matrix metalloproteinase would be beneficial, especially in the treatment of inflammatory diseases and autoimmune disorders.

Examples of inflammatory conditions and autoimmune disorders in which the compounds of the invention have potentially beneficial effects include diseases of the respiratory tract such as asthma (including allergen-induced asthmatic reactions), cystic fibrosis, bronchitis (including chronic bronchitis), chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), chronic pulmonary inflammation, rhinitis and upper respiratory tract inflammatory disorders (URID), ventilator induced lung injury, silicosis, pulmonary sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, arthritis, e.g. rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, Reiter's syndrome, gouty arthritis and prosthetic joint failure, gout, acute synovitis, spondylitis and non-articular inflammatory conditions, e.g. herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, inflammatory disorders of the

gastrointestinal tract, e.g. ulcerative colitis, diverticulitis, Crohn's disease, inflammatory bowel diseases, irritable bowel syndrome and gastritis, multiple sclerosis, systemic lupus erythematosus, scleroderma, autoimmune exocrinopathy, autoimmune encephalomyelitis, diabetes, tumor angiogenesis and metastasis, cancer including carcinoma of the breast, colon, rectum, lung, kidney, ovary, stomach, uterus, pancreas, liver, oral, laryngeal and prostate, melanoma, acute and chronic leukemia, periodontal disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy, muscle degeneration, inguinal hernia, retinal degeneration, diabetic retinopathy, macular degeneration, ocular inflammation, bone resorption diseases, osteoporosis, osteopetrosis, graft vs. host reaction, allograft rejections, sepsis, endotoxemia, toxic shock syndrome, tuberculosis, usual interstitial and cryptogenic organizing pneumonia, bacterial meningitis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, leishmaniasis, Lyme disease, glomerulonephritis, glomerulosclerosis, renal fibrosis, liver fibrosis, pancreatitis, hepatitis, endometriosis, pain, e.g. that associated with inflammation and/or trauma, inflammatory diseases of the skin, e.g. dermatitis, dermatosis, skin ulcers, psoriasis, eczema, systemic vasculitis, vascular dementia, thrombosis, atherosclerosis, restenosis, reperfusion injury, plaque calcification, myocarditis, aneurysm, stroke, pulmonary hypertension, left ventricular remodeling and heart failure.

Diseases of principal interest include COPD and inflammatory diseases of the respiratory tract and joints and vascular diseases.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable derivative thereof for use in medicine.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable derivative thereof for the manufacture of a medicament for the treatment of inflammatory conditions or autoimmune disorders.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject suffering from or susceptible to an autoimmune disorder or an inflammatory condition which method comprises administering to said human or animal subject an

effective amount of a compound of formula (I) or a physiologically functional derivative thereof.

5 The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising a compound of formula (I) or a physiologically acceptable derivative thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

10 There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

15 The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, topical, buccal, parenteral or rectal administration, preferably for oral administration.

20 Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily  
25 suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for  
30 example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl *p*-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Compounds according to the invention for topical administration may be formulated as creams, gels, ointments or lotions or as a transdermal patch. Such compositions may for example be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilising, dispersing, suspending, and/or colouring agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. They may also contain a preservative.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example anti-inflammatory agents (such as corticosteroids (e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide) or NSAIDs (e.g. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, CCR-3 antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or beta adrenergic agents (such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof) or anti-infective agents (e.g. antibiotics, antivirals).



It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.01 to 100mg/kg body weight, preferably 0.1 to 25 mg/kg body weight, more preferably 0.3 to 5mg/kg body weight,. The compounds may be given more than once daily to be equivalent to the total daily dose. The precise dose will of course depend on the age and condition of the patient and the particular route of administration chosen and will ultimately be at the discretion of the attendant physician.

No toxicological effects are expected when a compound according to the present invention is administered in the above mentioned dose range.

Compounds of the invention may be tested for *in vitro* activity in accordance with the following assay:

The fluorescent peptide substrate used in the MMP-12 assay is FAM-Gly-Pro-Leu-Gly-Leu-Phe-Ala-Arg-Lys(TAMRA), where FAM represents carboxyfluorescein, and TAMRA represents tetramethylrhodamine. MMP12 catalytic domain (residues 106-268) protein was expressed in *E. coli* in the form of insoluble inclusion bodies & stored in concentrated solution under denaturing conditions (8M guanidine hydrochloride). Enzyme was refolded into active form *in situ* by direct dilution into assay reactions. The 51 uL reactions are run in NUNC-brand black, square 384-well plates, each well containing 2 uM substrate, 20 nM enzyme, and 0.001-100 uM inhibitor, in 50 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM CaCl<sub>2</sub>, 1 uM ZnAc, 0.6 mM CHAPS, and 2 % DMSO. Postitive control wells contain no inhibitor. Negative control wells are effected by either pre-dispensing the EDTA quench (see below) or by omiting enyme. Reactions are incubated at ambient temperature for 120 min, then quenched by the addition of 15uL of 100mM EDTA. Product formation in each well is quantified by measuring flourescence with a Molecular Devices Acquest. The excitation wavelength is set at 485 nM, and the emmision wavelenght is 530 nM. IC<sub>50</sub> values were obtained by first calculating the percent inhibition (%I) at each inhibitor concentration (%I = 100\*(1-(I-C2)/(C1-C2)), where C1 is the mean of the positive controls, and C2 is the mean of the negative controls), then fitting the %I vs. inhibitor concentration [I] data to: %I=A+((B-A)/(1+((C/[I]^D))), where A is the lower asymptote, B is the upper asymptote, C is the IC50 value, and D is the slope factor. When tested in this assay, compounds of Examples 1 to 10 had IC50s below 100 micromolar.

The invention may be illustrated by reference to the following examples, which should not be construed as a limitation thereto:

## EXAMPLES

5

### General Experimental Details

LC/MS data were obtained under the following conditions:

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5 $\mu$ l
- Temp: RT
- UV Detection Range: 215 to 330nm

10

Solvents:     A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.  
                   B: 95% Acetonitrile + 0.05% Formic Acid

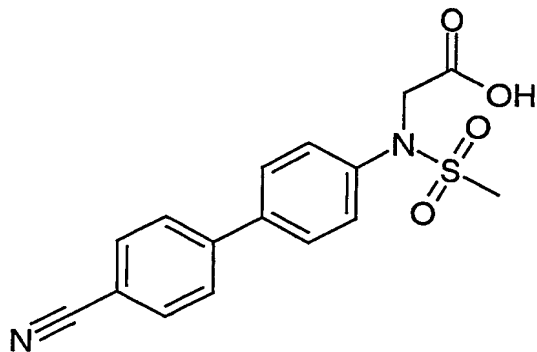
Gradient:	Time	A%	B%
	0.00	100	0
	0.70	100	0
	4.20	0	100
	5.30	0	100
	5.50	100	0

15

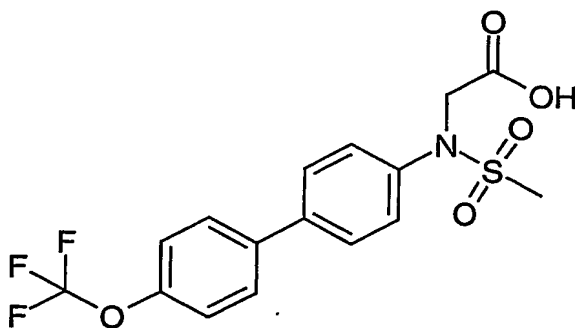
<sup>1</sup>HNMR spectra were obtained at 400 MHz on a Bruker-Spectrospin Ultrashield 400 spectrophotometer.

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All synthesis starting materials and reagents were used as obtained from commercial suppliers.

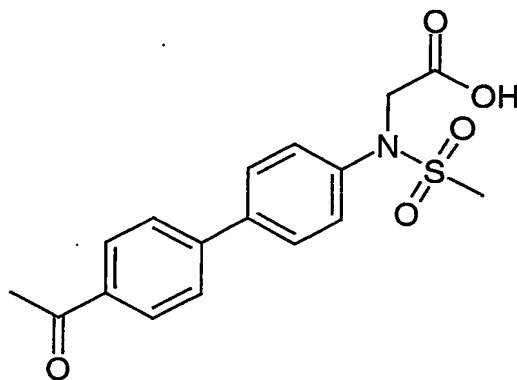
Example 1**[(4'-Cyano-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

5 A solution of [(4-bromophenyl)(methylsulfonyl)amino]acetic acid (intermediate 3, 20 mg, 65  $\mu$ mol) in dimethoxyethane (1 mL) was added in one portion to a mixture of 4-cyanophenyl-boronic acid (9.5 mg, 65  $\mu$ mol) and fibrecat FC1001 (2.71% Pd; 25 mg, 6.5  $\mu$ mol) in a Smith microwave reaction vial. Aqueous sodium carbonate solution (1.0 M; 130  $\mu$ L, 130  $\mu$ mol) was added and the vial capped. The crude reaction mixture was heated at 150  $^{\circ}$ C for 15 min using a Smith Synthesiser microwave reactor. On cooling the vial was opened and the contents were filtered through a Whatman 5  $\mu$ M filter tube, washing the filter cake with methanol (2x1 mL). The filtrate was evaporated and the resulting residue was purified using mass directed auto-preparative reverse phase HPLC to give the *title compound* (1.1 mg, 5 %) as a white solid. LC/MS: 2.94 min;  $z/e$  329, calcd (M-1) 329.  $^1$ H NMR (400 MHz: MeOD): 7.80 (4H), 7.75 (2H), 7.65 (2H), 4.45 (2H), 3.10 (3H).

Example 2**{(Methylsulfonyl)[4'-(trifluoromethoxy)-1,1'-biphenyl-4-yl]amino}acetic acid**

Prepared analogously to Example 1. LC/MS: 3.41 min;  $z/e$  407, calcd (M+18) 407.

Example 3

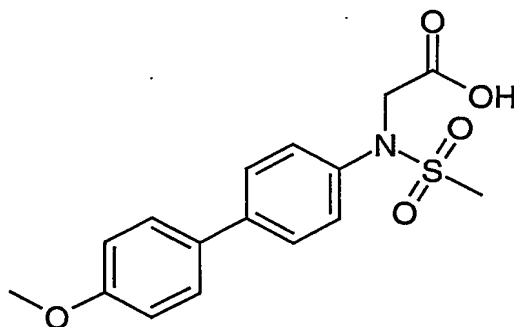


**[(4'-Acetyl-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

Prepared analogously to Example 1. LC/MS: 2.98 min;  $z/e$  365, calcd (M+18) 365.

5

Example 4

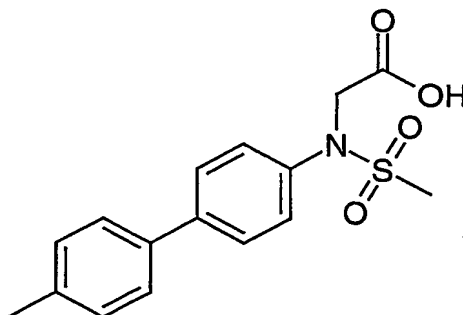


**[(4'-Methoxy-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

Prepared analogously to Example 1. LC/MS: 3.17 min;  $z/e$  353, calcd (M+18) 353.

10

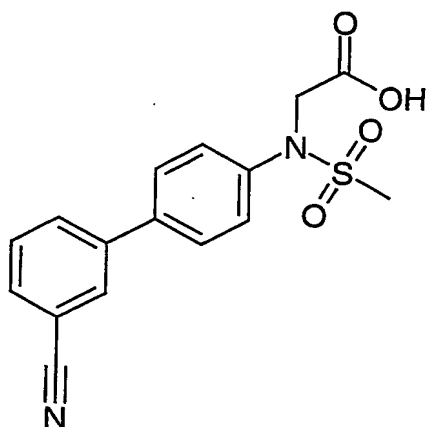
Example 5



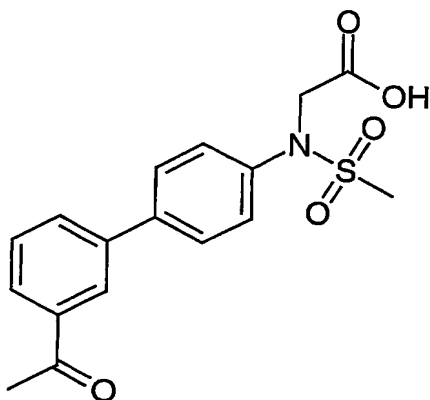
15

**[(4'-Methyl-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

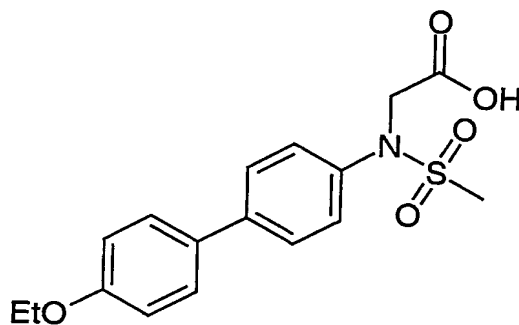
Prepared analogously to Example 1. LC/MS: 3.24 min;  $z/e$  337, calcd (M+18) 337.

Example 65 **[(3'-Cyano-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

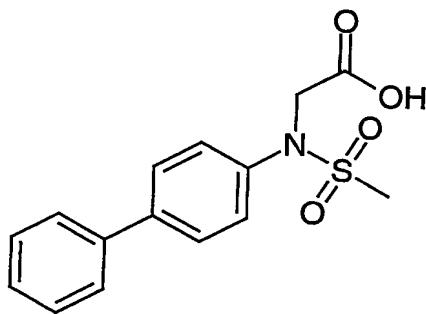
Prepared analogously to Example 1. LC/MS: 3.05 min; *z/e* 348, calcd (M+18) 348.

Example 7**[(3'-Acetyl-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

Prepared analogously to Example 1. LC/MS: 2.82 min; *z/e* 365, calcd (M+18) 365.

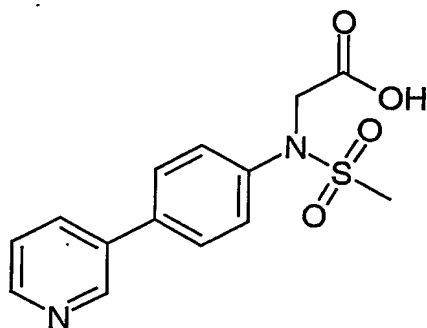
Example 8**[(4'-Ethoxy-1,1'-biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

5 Prepared analogously to Example 1. LC/MS: 3.24 min;  $z/e$  367, calcd (M+18) 367.

Example 9**[(1,1'-Biphenyl-4-yl)(methylsulfonyl)amino]acetic acid**

10 Prepared analogously to Example 1. LC/MS: 3.04 min;  $z/e$  323, calcd (M+18) 323.

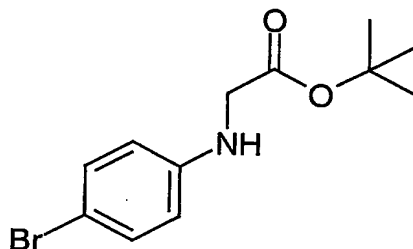
Example 10



5 **[(pyridin-3-ylphenyl-4-yl)(methylsulfonyl)amino]acetic acid (i.e. *N*-(methylsulfonyl)-*N*-(4-pyridin-3-ylphenyl)glycine)**

Prepared analogously to Example 1. LC/MS: 1.86 min; *z/e* 307, calcd (M+1) 307.

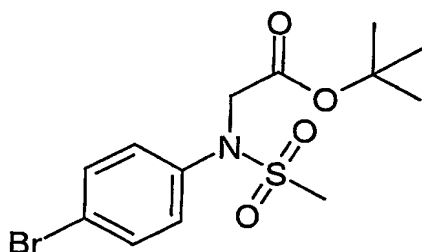
Intermediate 1



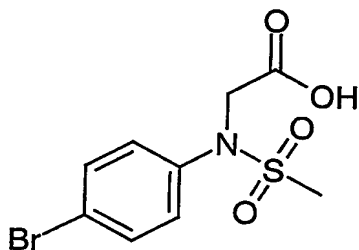
***tert*-Butyl [(4-bromophenyl)amino]acetate**

15 *t*-Butylbromoacetate (6.24 g, 4.72 mL, 32.0 mmol) was added in one portion to a stirred suspension of 4-bromonaniline (5.00 g, 29.1 mmol) and potassium carbonate (4.02 g, 29.1 mmol) in dimethylformamide (100 mL) at room temperature under nitrogen. The resulting mixture was stirred for 14 h then the volatiles were evaporated. The residue was partitioned between dichloromethane (50 mL) and water (50 mL). The aqueous phase was extracted with dichloromethane (3x50 mL) then the organic extracts were combined, dried

20 (magnesium sulfate) and the solvent evaporated. The residue was chromatographed on silica gel (20% ethyl acetate: cyclohexane) to give the *title compound* as a white solid (5.86 g, 70%). LC/MS: 3.65 min; *z/e* 286 and 288, calcd (M+1) 286 and 288. <sup>1</sup>H NMR (400 MHz: CDCl<sub>3</sub>): 7.30 (2H), 6.50 (2H), 4.35 (1H), 3.75 (2H), 1.45 (9H).

Intermediate 25 ***tert*-Butyl [(4-bromophenyl)(methylsulfonyl)amino]acetate**

A solution of *tert*-butyl [(4-bromophenyl)amino]acetate (intermediate 1, 5.86 g, 20.5 mmol), methanesulfonyl chloride (2.58 g, 1.74 mL, 22.5 mmol), triethylamine (4.15 g, 5.71 mL, 41.0 mmol) and 4-dimethylaminopyridine (260 mg, 2.05 mmol) in dichloromethane (100 mL) was heated at reflux for 14 h. A second portion of methanesulfonyl chloride (2.58 g, 1.74 mmol, 22.5 mmol) was added and heating at reflux continued for a further 48 h. The reaction was cooled to room temperature and extracted with aqueous hydrochloric acid solution (1.0 M; 3x50 mL). The organic phase was dried (magnesium sulfate) and evaporated to dryness. The residue was chromatographed on silica gel (10% diethyl ether: cyclohexane) to give the *title compound* as a pale cream solid (2.37 g, 32%). LC/MS: 3.35 min; *z/e* 381 and 383, calcd (M+18) 381 and 383. <sup>1</sup>H NMR (400 MHz: CDCl<sub>3</sub>): 7.55 (2H), 7.35 (2H), 4.30 (2H), 3.10 (3H), 1.45 (9H).

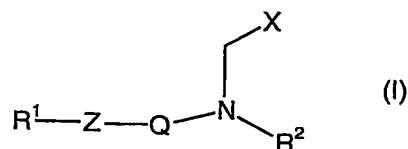
Intermediate 320 **[(4-Bromophenyl)(methylsulfonyl)amino]acetic acid**

A suspension of *tert*-butyl [(4-bromophenyl)(methylsulfonyl) amino]acetate (intermediate 2, 1.00 g, 2.74 mmol) and silica gel (13.7 g) in toluene (88 mL) was heated at reflux for 4 h. The reaction was cooled to room temperature and filtered, the filter cake was washed with methanol/ dichloromethane (20/80; 2x100 mL). Evaporation of the combined organic filtrates gave the *title compound* as a white solid (0.81 g, 95%). LC/MS: 2.81 min; *z/e* 325 and 327, calcd (M+18) 325 and 327. <sup>1</sup>H NMR (400 MHz: MeOD): 7.45 (2H), 7.35 (2H), 4.45 (2H), 3.05 (3H).



## CLAIMS

1. A compound of formula (I):



wherein

$\text{R}^1$  represents optionally substituted  $\text{C}_{4-12}$  alkyl, optionally substituted  $\text{C}_{2-6}$  alkylaryl, or optionally substituted 5- or 6- membered aryl or heteroaryl;

Z represents a bond,  $\text{CH}_2$ , O, S, SO,  $\text{SO}_2$ ,  $\text{NR}^4$ ,  $\text{OCR}^4\text{R}^5$ ,  $\text{CR}^4\text{R}^5\text{O}$ , or Z,  $\text{R}^1$  and Q together form an optionally substituted fused tricyclic group;

Q represents an optionally substituted 5- or 6- membered aryl or heteroaryl ring;

X represents  $\text{COR}^3$  or  $\text{N}(\text{OR}^8)\text{COR}^9$ ;

$\text{R}^2$  represents  $\text{SO}_2\text{R}^{10}$  or  $\text{SO}_2\text{NR}^{10}\text{R}^{11}$ ;

$\text{R}^3$  represents  $\text{OR}^6$ ,  $\text{NR}^6\text{R}^7$  or  $\text{NR}^6\text{OH}$ ;

$\text{R}^4$  and  $\text{R}^5$  each independently represents H,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{1-4}$  alkylaryl;

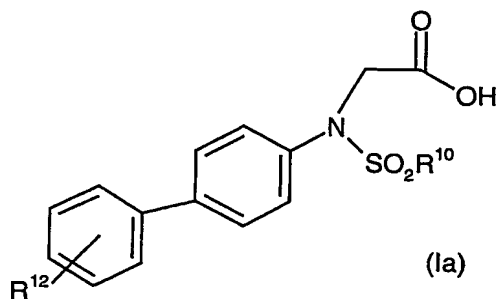
$\text{R}^6$  and  $\text{R}^7$  each independently represents H,  $\text{C}_{1-6}$  alkyl, or  $\text{C}_{1-6}$  alkyl substituted with one or more heteroaryl groups, or  $\text{R}^6$  and  $\text{R}^7$  together with the nitrogen atom to which they are attached form a 5- or 6- membered ring which may optionally include 1 or more further heteroatoms selected from O, S and N;

$\text{R}^8$  and  $\text{R}^9$  each independently represents H or  $\text{C}_{1-6}$  alkyl;

$\text{R}^{10}$  and  $\text{R}^{11}$  each independently represents H or  $\text{C}_{1-6}$  alkyl; and

and physiologically functional derivatives thereof, with the exception of N-(ethoxycarbonyl)-N-[4-(1H-tetrazol-1-yl)phenyl]glycine.

2. A compound as claimed in claim 1 of formula (Ia):



wherein  $R^{10}$  represents H or  $C_{1-6}$  alkyl;

$R^{12}$  represents H, halo,  $CF_3$ , cyano,  $OCF_3$ , nitro,  $OR^{13}$ ,  $SR^{13}$  or  $COR^{13}$ ;

$R^{13}$  represents H,  $C_{1-6}$  alkyl or  $C_{1-4}$  alkylaryl;

and physiologically functional derivatives thereof.

5

3. A compound as claimed in claim 1 or claim 2 for use in medicine.

10

4. A method for the treatment of a human or animal subject suffering from or susceptible to an autoimmune disorder or an inflammatory condition which method comprises administering to said human or animal subject an effective amount of a compound as claimed in claim 1 or claim 2.

15

5. The use of a compound as claimed in claim 1 or claim 2 for the manufacture of a medicament for the treatment of inflammatory conditions or autoimmune disorders.

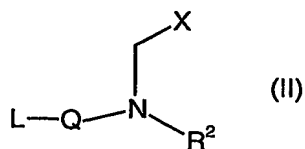
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6. A pharmaceutical composition comprising a compound as claimed in claim 1 or claim 2 and a pharmaceutically acceptable carrier therefor, and optionally one or more other therapeutic agents.

25

7. A process for the preparation of compounds of formula (I) as defined in claim 1, which process comprises:

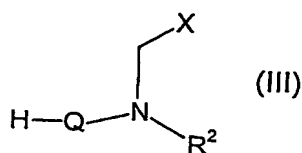
(A) for the preparation of a compound of formula (I) wherein Z represents a bond and  $R^1$  represents an optionally substituted  $C_{2-6}$  alkylaryl or an optionally substituted 5- or 6-membered aryl or heteroaryl, reacting a compound of formula (II):



wherein  $R^2$ , Q and X are as previously defined for formula (I) and L represents a leaving group, with a reagent suitable to introduce the group  $R^1$ ; or

30

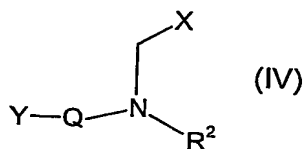
(B) for the preparation of a compound of formula (I) wherein Z represents a bond and  $R^1$  represents an optionally substituted  $C_{4-12}$  alkyl, reacting a compound of formula (III):



wherein  $\text{R}^2$ , Q and X are as previously defined for formula (I), with a reagent suitable to introduce the group  $\text{R}^1$ ; or

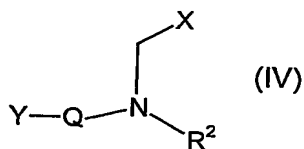
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(C) for the preparation of a compound of formula (I) wherein Z represents O, S, SO,  $\text{SO}_2$ ,  $\text{NR}^4$  or  $\text{OCR}^4\text{R}^5$ , and  $\text{R}^1$  represents an optionally substituted  $\text{C}_{4-12}$ alkyl, reacting a compound of formula (IV):



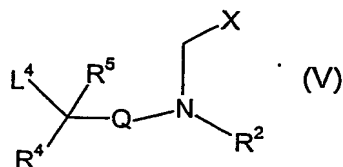
10 wherein X,  $\text{R}^2$  and Q are as previously defined for formula (I), and Y represents OH, SH,  $\text{NR}^4\text{H}$  or  $\text{HCR}^4\text{R}^5$ , with a reagent suitable to introduce the group  $\text{R}^1$  followed in the case where Y is SH by optional oxidation of the sulphide to the sulfoxide or the sulfone; or

15 (D) for the preparation of a compound of formula (I) wherein Z represents O, S, SO,  $\text{SO}_2$ , or  $\text{NR}^4$ , and  $\text{R}^1$  represents an optionally substituted  $\text{C}_{2-6}$ alkylaryl or an optionally substituted 5- or 6- membered aryl or heteroaryl, reacting a compound of formula (IV):



20 wherein X,  $\text{R}^2$  and Q are as previously defined for formula (I), and Y represents OH, SH or  $\text{NR}^4\text{H}$ , with a reagent suitable to couple to the group  $\text{R}^1$ , followed in the case where Y is SH by optional oxidation of the sulphide to the sulfoxide or the sulfone; or

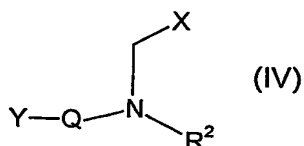
(E) for the preparation of a compound of formula (I) wherein Z represents  $\text{OCR}^4\text{R}^5$  and  $\text{R}^1$  represents an optionally substituted  $\text{C}_{2-6}$ alkylaryl or an optionally substituted 5- or 6- membered aryl or heteroaryl, reacting a compound of formula (V):



wherein X, R<sup>2</sup> and Q are as previously defined for formula (I) and L<sup>4</sup> is a suitable leaving group, with a reagent suitable to introduce the group R<sup>1</sup>-O; or

5

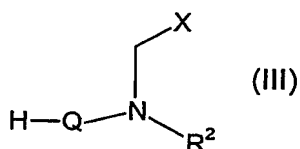
(F) for the preparation of a compound of formula (I) wherein Z represents CR<sup>4</sup>R<sup>5</sup>O, reacting a compound of formula (IV) :



wherein R<sup>2</sup> and Q are as previously defined for formula (I), and Y represents OH, with a reagent suitable to introduce the group R<sup>1</sup>CR<sup>4</sup>R<sup>5</sup>-; or

10

(G) for the preparation of a compound of formula (I) wherein Z represents CH<sub>2</sub>, comprises reacting a compound of formula (III):

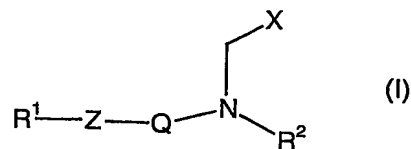


15 wherein R<sup>2</sup>, Q and X are as previously defined for formula (I), with a reagent suitable to introduce the group R<sup>1</sup>CH<sub>2</sub>; or

(H) comprises carrying out a process selected from processes (A) to (G) followed by interconversion of one or more functional groups.

**ABSTRACT****Therapeutically Useful Compounds**

5 Compounds of formula (I):



wherein

R<sup>1</sup> represents optionally substituted C<sub>4-12</sub> alkyl, optionally substituted C<sub>2-6</sub>alkylaryl, or optionally substituted 5- or 6- membered aryl or heteroaryl;

10 Z represents a bond, CH<sub>2</sub>, O, S, SO, SO<sub>2</sub>, NR<sup>4</sup>, OCR<sup>4</sup>R<sup>5</sup>, CR<sup>4</sup>R<sup>5</sup>O, or Z, R<sup>1</sup> and Q together form an optionally substituted fused tricyclic group;

Q represents an optionally substituted 5- or 6- membered aryl or heteroaryl ring;

X represents COR<sup>3</sup> or N(OR<sup>8</sup>)COR<sup>9</sup>;

R<sup>2</sup> represents SO<sub>2</sub>R<sup>10</sup> or SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>;

R<sup>3</sup> represents OR<sup>6</sup>, NR<sup>6</sup>R<sup>7</sup> or NR<sup>6</sup>OH;

15 R<sup>4</sup> and R<sup>5</sup> each independently represents H, C<sub>1-6</sub> alkyl or C<sub>1-4</sub> alkylaryl;

R<sup>6</sup> and R<sup>7</sup> each independently represents H, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted with one or more heteroaryl groups, or R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which they are attached form a 5- or 6- membered ring which may optionally include 1 or more further heteroatoms selected from O, S and N;

20 R<sup>8</sup> and R<sup>9</sup> each independently represents H or C<sub>1-6</sub> alkyl;

R<sup>10</sup> and R<sup>11</sup> each independently represents H or C<sub>1-6</sub> alkyl; and

and physiologically functional derivatives thereof, with the exception of N-(ethoxycarbonyl)-N-[4-(1H-tetrazol-1-yl)phenyl]glycine, processes for their preparation, pharmaceutical

25 formulations containing them and their use as inhibitors of matrix metalloproteinase enzymes (MMPs) are described.

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